Meeting Minutes

Meeting Date: February 6, 2002 **Time:** 4:00PM **Location:** MPN II, CR B

ANDA and Drug Name: NDA 18-662 (Accutane (isotretinoin) Capsules)

External participant: Hoffmann La Roche Inc.

Type of meeting: External

Meeting Chair: Gary Buehler, Director, OGD

External participant lead: George Abercrombie, Hoffmann La Roche Inc.

Meeting Recorder: Sarah Ho, Project Manager, OGD

FDA Attendees, titles and offices (see attached attendance lists):

Fred Ansell	OCC, GCF-1
Ginny Beakes	Supervisor, Regulatory Counsel, DRPII, ORP
Julie Beitz (via telephone)	Director, DDRE, ODS
Allen Brinker (via telephone)	Medical Epidemiology, Epidemiologist, DDRE, ODS
Gary Buehler	Director, OGD
Jonca Bull	HFD-105
James Fan	Team Leader, Division of Chemistry I, OGD
Lillie Golson	Reviewer, Division of Labeling, OGD
John Grace	Team Leader, Division of Labeling, OGD
Patrick Guinn (via telephone)	Project Manager, DDRE, ODS
Rita Hassall	Special Assistant, OGD
Don Hare	OGD
Sarah Ho	Project Manager, DLPS, OGD
Mary Jean Kozma-Fornaro	SCSO, DDDDP, OND
Lee Lemley	EOS
Marilyn Pitts (via telephone)	Safety Evaluator, DDRE, ODS
Terri Rumble	Supervisor, Consumer Saftey Officer, DRUDP, OND
Ann Simoneau	Regulatory Counsel, DRPII, ORP
Anne Trontell	Division Director, DSRCS
Robert West	Acting Deputy Director, OGD
Lynn Whipkey	OCC, GCF-1
Jonathan Wilkin	HFD-540

External constituents and affiliation (see attached attendance lists):

George Abercrombie	Hoffmann La Roche Inc.
Susan Ackermann	Hoffmann La Roche Inc.
Charles Clark	CPR communications

Cindy Dinella	Hoffmann La Roche Inc.
Russell Ellison	Hoffmann La Roche Inc.
Georges Gemayel	Hoffmann La Roche Inc.
Martin Hanicutt	Bertek Pharmaceuticals, Inc.
Rick Kentz	Hoffmann La Roche Inc.
Fred Killion	Barr Laboratories, Inc.
John E. Laflore	Hoffmann La Roche Inc.
Rulie McMurray	Hoffmann La Roche Inc.
Allen Mitchell (via telephone)	Slone Epidemiology – Boston University
Christine Mundkur	Barr Laboratories, Inc.
John O'Donnell	Mylan Pharmaceuticals Inc.
Abha Pant (via telephone)	Ranbaxy Pharmaceuticals Inc.
Salvatore Peritore	Barr Laboratories, Inc.
Robert Pollock (via telephone)	Lachman Consultant Services
Tammy Reilly	Hoffmann La Roche Inc.
Joanne Richerdson	Genpharm Inc.
Jim Sherry	Bertek Pharmaceuticals, Inc.
Patricia Strasser (via telephone)	Ranbaxy Pharmaceuticals Inc.
Joanna Waugh	Hoffmann La Roche Inc.

Meeting Objectives (as delineated by Roche by letter dated November 5, 2001):

1. To gain common understanding on the potential areas which could compromise 1) the viability and integrity of the S.M.A.R.T. program; and 2) its accompanying surveillance system when multiple isotretinoin products become available.
2. To discuss FDA-proposed solutions to the potential areas of concern that have been identified, thus maintaining the viability and integrity of the S.M.A.R.T. program when other isotretinoin products come to market.
3. To agree on intentions for specific responsibility and accountability of each manufacturer for its own program when multiple risk management programs become available.

Discussion Points:

1. Mr. Buehler announced that the minutes of this meeting will be available on the public docket because the issues to be discussed were similar to those in the citizen's petition submitted by Roche, February 5, 2002.

2. Representatives from Roche introduced the issues. They expressed concern that their S.M.A.R.T. program would fail if these issues were not resolved prior to isotretinoin availability in a multi-source environment. Therefore, they wanted to address these issues prior to the approval of generic isotretinoin products. They conveyed the belief that safety in a multi-source environment had not been addressed.

The following points address the questions submitted by Roche prior to the meeting. (Attached)

3. **Program Elements**

FDA indicated that:

- All manufacturers will be required to model their labeling after Roche's copyrighted educational materials ("Guide to Best Practices Brochure", etc.) since all of the educational materials are considered part of labeling.

- All manufacturers will be required to have all educational pieces printed and approved prior to launch. This includes all pieces listed in the October 30, 2001 supplement approval letter for Accutane.

- All manufacturers will be placing the medication guide in their packaging.

- All manufacturers will be using the same text on their packages as Roche.

A question was raised as to whether FDA would be monitoring the dissemination of materials. This related to possible product differentiation. It was stated that FDA does not have the capacity to do so.

4. **Physician Database**

Roche representatives expressed a concern that the pharmacist will not know which firm to call to verify that a physician was qualified to dispense isotretinoin. They were interested in the ability to link the physician with the appropriate database. Dr. Wilkin indicated that this aspect of the program would require some clarification over time. It was noted that physicians will need to attest to having read the material from any manufacturer. Dr. Wilkin questioned how frequently it would be necessary for the pharmacist to verify the physician's qualification.

5. **Accutane Survey**

FDA indicated that all manufacturers will be required to have a survey protocol and questionnaire in place when their product is marketed. It was assumed that the questionnaire will be identical. Roche representatives stated that they viewed the Slone group as their vendor. Dr. Mitchell of the Slone group clarified that the Slone group represents itself and that the survey may be applicable to a number of products. Dr. Wilkin indicated that the approval letter was speaking of the kind of survey conducted by Slone and that Accutane is isotretinoin. The approval letter did not specify the particulars of this survey.

Regarding the question of whether all manufacturers would need to demonstrate the representativeness of the user population for the female survey, FDA noted that generics should have a patient based survey in place to address the critical elements. The content of the survey was of concern. Dr. Trontell added that there is no formula for representativeness.

FDA indicated that all manufacturers would be required to enroll women via three modes: blister pack, in the physician's office, and by telephone, even though these three modes were not specified in the approval letter. The aim was and will be to increase enrollment overall. Roche expressed concern that if the enrollment is pooled and other manufacturers are not as diligent, the metrics will not be met. Dr. Mitchell was of the opinion that there should be standardization of enrollment methods.

Roche representatives expressed the desire to have a method in place to differentiate products vis-à-vis enrollment materials received by the physician. Dr. Trontell stated that the survey probably does not distinguish manufacturers but will probably ask the patient what product the patient received. Dr. Mitchell indicated that he hopes to identify the manufacturer on the forms via a code or a logo.

Dr. Mitchell noted that the landscape changes with multiple products on the market, and that no one necessarily knows the answers to all the questions. He also stated that there are sets of questions in the survey about what materials that were used and the product received. Dr. Mitchell indicated that there are families of data that can be evaluated and sees it as an evolving story.

Roche representatives summed up their concerns into three primary issues: re-enrollment of patients, the reliability of the data, and the question of whether there would be a different patient population for different manufacturers. They questioned whether there would be a solution before entering into a multi-source environment. They also questioned whether FDA would validate the methodology for de-duplication of survey enrollees.

Dr. Wilkin suggested that an internal focus meeting on this topic would be helpful. He noted that a common system is the ideal.

Dr. Trontell stated that it is preferable to have the denominator for the survey calculated in one constant manner. Roche representatives asked when this would be worked out. Dr. Trontell stated that an approach would be determined, but that it may not be by April 10, 2002. In addition, she stated that since this is an analytic issue and not part of the survey, it did not necessarily have to be determined by that date. Roche representatives disagreed expressing belief that it should not be a retrospective issue.

Dr. Wilkin suggested that a focus meeting on this topic would be helpful as well.

6. **Questions Specific to Roche**

FDA indicated that the Roche labeling would not need to be changed unless the division required it for some reason.

FDA indicated that the quarterly reporting would not need to be changed. All manufacturers will be required to provide the special reports regarding pregnancy and congenital abnormalities. Dr. Wilkin did not recall that there was a requirement for a two year

pregnancy follow-up, either through the end of an aborted pregnancy or for one year after birth. FDA and Roche will check their files to determine if this is still a requirement.

FDA indicated that all manufacturers would need to follow-up in regards to the psychiatric risk management components. The innovator will have sole responsibility for the psychiatric prospective clinical trial.

Dr. Wilkin noted that there might need to be some provision for a special message regarding generic products being the same as Accutane in the generic product label. This will be decided at a later date.

7. **Pharmacy Survey Outcome Measures**

Dr. Trontell stated that the specifics of the pharmacy survey need to be determined. It was also stated that Roche's method for this survey would be a sampling of all the pharmacies and that this method may not be the best method. Therefore, FDA would not want to hold the other manufacturers to this method.

Roche representatives stated that they will only audit Accutane dispensed prescriptions. If a prescription is written for Accutane and a generic is dispensed then they will not count that prescription in their audit. However, if a prescription is written for isotretinoin and Accutane is dispensed then they will count that prescription in their audit.

Dr. Trontell noted that the goal of this survey is to have a collaborative effort in measuring the success of the program.

Dr. Bull suggested that this topic be revisited at a later time.

FDA indicated that all manufacturers will have a protocol in place prior to launch. All manufacturers' stickers will be yellow. The verbiage of the stickers would be similar.

Unresolved issues or issues requiring further discussion:

1. Can other manufacturers use Roche's copyrighted pregnancy symbol? It is not clear as to whether this symbol is Roche's alone.
2. How will the different manufacturers be distinguished in the Accutane Survey? How do we prevent duplication of enrollees? How can we assure reliability of the data? Would different manufacturers capture different patient populations? How is the denominator for each manufacturer going to be calculated?
3. Will there be some provision for a special message regarding generic products being the same as Accutane in the generic product label?
4. How should the pharmacy survey be carried out? What are the specifics of this survey? How is FDA going to ensure non-overlap of pharmacy samples in the audit? How is FDA going to minimize pharmacist frustrations with audit sampling?

Action Items:

1. Roche and the agency will go back through the Accutane file to determine if the two-year pregnancy follow-up is a requirement.
2. Follow-up internal meetings on enrollment of patients in the Slone survey, determination of the denominator calculation, and further clarification of the Pharmacy survey need to be scheduled.

Signature, minutes preparer: _____ 3/4/02

Concurrence Chair (or designated signatory): _____ 3/5/02

Attachments/Handouts: Attendance lists
Roche letter dated November 5, 2001
Questions submitted by Roche

CC: ANDA 75-945
ANDA 76-041
ANDA 76-135
ANDA 76-293
NDA 18-662
Division File
Field Copy
HFD-007/G. Beakes
GCF-1/F. Ansell

Endosements:

HFD-600/G. Buehler
HFD-600/R. West
HFD-600/R. Hassall
HFD-613/J. Grace
HFD-613/L. Golson/2/22/02
HFD-623/J. Fan
HFD-617/S. Ho/2/22/02

HFD-105/J. Bull/2/21/02
HFD-540/J. Wilkin/3/3/02
HFD-430/A. Trontell/2/21/02
HFD-430/J.Beitz/2/21/02

Draft by: S. Ho/2/22/02
Final Type by: S. Ho/3/4/02

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MEETING ATTENDEES

DATE: 2/6/02 PRODUCT: Isotretinoin

NAME	AFFILIATION
John E. LaFlore	Roche
Susan D. Akerman	Roche
Cindy Pinella	Roche
George Abercrombie	Roche
Russell Ellison	Roche
Rick Kentz	Roche
Tammy Reilly	Roche
Julie L. McMurray	Roche
Joanna Waugh	Roche
Georges Renard	Roche

MEETING ATTENDEES

DATE: 2/6/02 PRODUCT: Isotretinoin

NAME	AFFILIATION
CHRISTINE MUNDKUR	BARR LABORATORIES
FRED KILLION	"
SAL PERITORE	BARR LABORATORIES
Frank Sisto	Mylan Pharmaceuticals
JO-ANNE RICHARDSON	GENPHARM INC
Lita Rhassall	OGD-FDA

MEETING ATTENDEES

DATE: 2/6/02 PRODUCT: Isotretinoin

NAME	AFFILIATION
Ann Dunnenan	OTRP
Gayle Bakes	OTRP
Lilli Olson	OGD
Sarah Ho	OGD
Gary Buehler	OGD
John F. Grace	OGD
Terri Rumble	HFD-105
Lee Henley	EOS
Maureen Dreher	HFD 540
Robert Lee Jest	OGD HFD-601
Lynn Whipkey	OCC - GCF-1
Fred Ansell	OCC-GCF-1
Jan Hart	OGD-604
JONATHAN WILKIN	HFD 540
Tonia Bull	HFD 105
Anne Trontell	HFD 430
Martin Hemwitt	Bertek
Charles Clark	CPR Communications
Jim Sherry	Bertek Pharmaceuticals, Inc.
John O'Donnell	Mylan Bloom
James Fan	HFD/OGD

November 5, 2001

Dr. Jonathan Wilkin
Food and Drug Administration
Division of Dermatologic & Dental Drug Products, HFD-540
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Office of Drug Evaluation V
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Rockville, Maryland 20850

CONFIDENTIAL AND PROPRIETARY

Dear Dr. Wilkin:

Re: **NDA 18-662 – Accutane (isotretinoin) Capsules - S-044 System to Manage Accutane Related Teratogenicity (S.M.A.R.T.). Request for Meeting**

We refer to the approval of the above supplemental application on October 30, 2001 which provided for revisions to the labeling to reflect the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) Program, an enhanced risk management program with the public health goal of helping to prevent fetal exposure to Accutane.

As discussed with FDA during the review of the S.M.A.R.T. program, Roche has however, identified several areas of concern that will arise when multiple isotretinoin products are available on the marketplace with other S.M.A.R.T.- like programs. The attached document describes some of these concerns.

We would like to request a meeting with FDA to discuss issues relating to the potential public health consequences of having multiple isotretinoin products on the market. We want to work with FDA to assure that the public health goals we share are not compromised in a multi-product marketplace.

We propose the following objectives for such a discussion:

- To gain common understanding on the potential areas which could compromise 1) the viability and integrity of the S.M.A.R.T. program; and 2) its accompanying surveillance system when multiple isotretinion products become available.
- To discuss FDA-proposed solutions to the potential areas of concern that have been identified, thus maintaining the viability and integrity of the S.M.A.R.T program when other isotretinoin products come to market.
- To agree on intentions for specific responsibility and accountability of each manufacturer for their own program when multiple risk management programs become available.

Should you have any questions, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Cynthia Dinella
Vice President
Drug Regulatory Affairs
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CD/gb

HLR No. 2001-2548

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Ms. Mary Jean Kozma-Fornaro, Sr. Sup. Reg.,HFD-540
Dr. Janet Woodcock, Director CDER, HFD-001
Dr. Sandra Kweder, Medical Officer, HFD-022
Dr. Steven Galson, Deputy Center. Director, HFD-001
Dr. Jonathan Wilkin, Sup. Medical Officer, HFD-540
Dr. Kathryn O'Connell, Medical Officer, HFD-540

1. INTRODUCTION

Roche is committed to appropriate risk management to ensure the safe and effective use of Accutane. Roche has worked closely with FDA to develop and implement a comprehensive program that specifically addresses the area of pregnancy prevention. FDA and Roche have agreed no woman should start Accutane while being pregnant and that no woman should become pregnant while on Accutane. Roche believes that this pregnancy prevention program, including the assessment of such, as outlined in the Accutane Label Supplement Approval Letter (October 30, 2001), is an effective program for Accutane to meet these overall public health goals. Under the new program:

- a new yellow Accutane Qualification Sticker should be attached to the prescriber's regular prescription form to indicate the patient has been qualified to receive Accutane,
- all female patients must have two negative pregnancy tests as well as education about pregnancy before their first Accutane prescription,
- no Accutane prescriptions will be given for more than one month supply at a time and the patient must have a new negative pregnancy test before each new prescription,
- all female patients who are, or might become, sexually active with a male partner must use two forms of effective contraception simultaneously for at least one month prior to starting Accutane, during therapy, and for one month following discontinuation of the drug, and
- pharmacists will dispense Accutane only on receiving a prescription with the special Accutane sticker. Requests for refills without a new prescription and phoned-in prescriptions will not be filled.

Through the "System to Manage Accutane Related Teratogenicity" (S.M.A.R.T.) program, Roche has established a system to respond more quickly to these public health goals, while at the same time assuring high data standards and patient confidentiality. Furthermore, the Accutane pregnancy prevention risk management program will be assessed through a series of metrics, which are specific to key aspects of the S.M.A.R.T. program. FDA made clear in the October 30, 2001 Accutane Label Supplement Approval Letter that the S.M.A.R.T. program is a mandatory component of the Accutane Label.

Without full resolution of the issues addressed in this document, we are concerned about the ability of FDA, Roche, and other companies to maintain these high standards in a multiple isotretinoin product environment.

Roche's isotretinoin patent, as extended by pediatric exclusivity, expires on February 7, 2002. It is possible that isotretinoin products manufactured by other companies may be approved at that time. Roche assumes that the manufacturer of any isotretinoin product approved through an abbreviated new drug application (ANDA) will be required to implement a pregnancy prevention risk management program identical to the S.M.A.R.T.™ program in all material respects, in accordance with the statutory requirement that an ANDA drug bear labeling that is the same as that of the listed drug. We are concerned, however, that the simultaneous availability of multiple isotretinoin products supported by identical S.M.A.R.T.-like programs threatens to compromise the viability and integrity of any one of those programs. This has become increasingly clear to us

as we have enhanced and refined the pregnancy prevention program that was already in place. Roche recognizes that this poses a challenge to FDA in carrying out its statutory mandate to protect the public health in an environment in which multiple isotretinoin products may be distributed by different manufacturers.

In brief, there is a fundamental implementation difficulty presented by state generic substitution laws. Assuming that the healthcare provider writes a prescription for Accutane, this generally will be substitutable at the pharmacy with any AB-rated isotretinoin product unless the healthcare provider requires that the brand be dispensed in accordance with state law. Thus, although the healthcare provider writes the prescription for Accutane (using yellow self-adhesive Accutane Qualification Sticker), obtains the necessary negative pregnancy tests, helps the female patient choose two safe and effective forms of contraception, obtains informed consent, seeks to enroll the patient in the Accutane Survey, and follows the other requirements of the pregnancy prevention risk management program, the healthcare provider will not have any way of knowing which manufacturer's product actually will be dispensed to and used by the patient (unless the prescriber prohibits substitution in accordance with states laws, which can vary from state to state). Furthermore, there is no way of knowing which surveillance program the female patient enrolls in, or if she enrolls in more than one. The issues multiply when consideration is given to the fact that subsequent prescriptions in the same course of therapy may be filled with products of different manufacturers, so there is no assurance of consistency for any single patient. This confusion will be further compounded by the fact that the S.M.A.R.T. process depends upon reliable metrics to guide the continual evaluation of this pregnancy prevention risk management strategy.

Roche has identified several areas of concern regarding the availability of multiple isotretinoin products, including: (1) public health surveillance, i.e., metrics; (2) healthcare provider and patient compliance with regard to which pregnancy prevention program they are participating in; and (3) reproducibility of Roche's current program of education, training and expertise. Therefore, we request to initiate a dialogue with the Agency to determine how FDA will ensure that the public health goals it shares with Roche are not compromised by the presence of multiple forms of isotretinoin. That is to say, how the program that Roche puts in place can be adequately tracked and measured in a real world situation and then potentially modified to meet the goal that no woman should start Accutane while being pregnant and no woman should become pregnant while on Accutane. Therefore, it is imperative that Roche has an accurate numerator and denominator in order to scientifically determine which components of the S.M.A.R.T. program are working appropriately and which need to be emphasized with the prescriber, pharmacist and / or patient. Roche is committed to working closely with FDA to identify issues relating to the public health consequences of having multiple isotretinoin products on the market.

2. PUBLIC HEALTH SURVEILLANCE

Roche's S.M.A.R.T. program contains several discrete requirements that must be fulfilled by the healthcare provider, pharmacist, and patient. The program is initiated with the healthcare provider joining S.M.A.R.T. by completing the Letter of Understanding, reading the Guide to Best Practices, and receiving yellow self-adhesive Accutane Qualification Stickers. He/she also may attend an optional Roche-sponsored CME/CEU that specifically addresses the risks associated with Accutane therapy and the proper use and prescribing of the product in order to

reduce or eliminate these risks. The healthcare provider then confirms that the female patient of childbearing potential has been qualified to receive a prescription for Accutane through assurance of negative pregnancy test(s); provides appropriate counseling to her on the choice and use of two forms of safe and effective contraception; encourages her to register in the Accutane Survey (Slone); and ensures that she reads, understands, and signs the Accutane Patient Information/Informed Consent. When the female patient appears at the pharmacy with her Accutane prescription, the pharmacist will only fill an Accutane prescription if the yellow self-adhesive Qualification Sticker is affixed, dispense no more than a one-month supply, and dispense the product with an Accutane Medication Guide. This entire process is repeated for each of the patient's Accutane prescriptions throughout the course of her therapy (see Appendix 1). Clearly, all parties in this prescribing chain share responsibility for the safe and effective use of Accutane.

To construct a balanced and reliable assessment of this comprehensive and multi-faceted pregnancy prevention risk management program, Roche has developed a system to obtain relevant information from all constituent stakeholders. This comprehensive program evaluation system consists of the longitudinal Accutane Survey (Slone), the point-in-time DMD pharmacy audit, and a 3rd metric (to be agreed upon between Roche and FDA). With multiple isotretinoin products on the market, the risk of confounding both the numerator and denominator of each of these metrics is high. For example, substitution at the pharmacy level will make it impossible to determine the average length of therapy. As no refills are allowed with isotretinoin, if a female patient starts her course of therapy on Accutane but completes her course of therapy on another manufacturer's product, she will be counted as a new patient start for both Accutane and the other manufacturer's product. Therefore, her course of therapy will be one month for Accutane and n-1 months for the other manufacturer's product. Switching at the pharmacy level presents the most significant issue to the integrity of the risk management program. IMS-Health data, for example, has shown that so far in 2001, 74% of all prescriptions written for Klonopin are filled with another manufacturer's product.

As FDA is fully aware, no isotretinoin pregnancy prevention risk management program can be adequately assessed unless each manufacturer has as accurate assessment of the number of female patients on its product, the number of female patients enrolled in its program, and the characteristics of their female patients. Inaccurate counting is likely to result if a prescription is substituted at the pharmacy level. Scenarios might arise where the metrics could be artificially exceeded or unmet depending on who is considered part of the numerator and who is considered part of the denominator. For example:

- If a female patient signs up for the Accutane S.M.A.R.T. program, receives a prescription for Accutane, and fills the prescription for Accutane, her data will be correctly counted in both the Accutane numerator and denominator.

- If a female patient signs up for the Accutane S.M.A.R.T. program, receives a prescription for Accutane, and has it substituted at the pharmacy for another manufacturer's product, her data will be incorrectly counted in the Accutane numerator, correctly excluded from the Accutane denominator, correctly counted in the other manufacturer's product's denominator and incorrectly excluded from the other manufacturer's numerator.

- If a female patient signs up for the Accutane S.M.A.R.T. program, receives a prescription for Accutane, and has her first prescription filled as Accutane and her subsequent prescriptions filled with another manufacturer's products, her data will be correctly counted in the Accutane numerator (and potentially in the other manufacturer's product's numerator) and incorrectly counted in both the Accutane and another manufacturer's product's denominator.

The above examples provide just a few of many possible scenarios. The numerator could be further confounded if the female patient registers for more than one pregnancy prevention program during the same course of treatment

2.1 Potential for Pharmacy Substitution

Given the potential to confound each manufacturer's numerator and denominator, options must be explored to minimize confusion and / or prevent switching at the pharmacy level. One way to partially mitigate this situation would be placing a mandatory "dispense as written" or "brand medically necessary" on each of the yellow self-adhesive Accutane Qualification Stickers. However, due to mandatory substitution laws and formulary restrictions, this will not completely solve the problem.

3. HEALTHCARE PROVIDER AND PATIENT COMPLIANCE

The S.M.A.R.T. program was designed during a period with only one isotretinoin product on the market, i.e. Accutane. Consequently, there could be potential for confusion when other isotretinoin product(s) enter the market. This confusion could potentially affect both the healthcare provider and the patient.

The yellow self-adhesive Accutane Qualification Sticker is critical documentation linking an Accutane prescription to two negative pregnancy tests, the use of two safe and effective forms of contraception, understanding and signing the Accutane Patient Information/Informed Consent, and offering enrollment in the Accutane Survey (Slone). This linkage is an important risk management step, in addition to the other steps necessary to qualify a patient to receive a prescription for Accutane. If a female patient is familiar with one qualification sticker and receives another, she may be unsure of which product she is taking and may, in her confusion, enroll in and complete a survey for a product she was not prescribed or may complete more than one manufacturer's survey. Questions relating to the correct linkage of adverse events with a particular manufacture's products also are raised. While the issue of appropriate reporting arises in other multiple-manufacturer scenarios, it rarely is of any regulatory significance because most times it can be corrected through a labeling modification, which all versions of the product would carry. In the case of isotretinoin, however, accurate reporting is critical in determining the success or failure of each manufacturer's individual pregnancy prevention risk management program, which ultimately relates to the overall public health goals.

Additionally, multiple isotretinoin products will presumably require healthcare providers to have more than one isotretinoin pregnancy prevention risk management program available in their office. There may be confusion as to which manufacturer's program to use, which contraceptive counseling line to call, or which manufacturer to query should a medical question or safety concern arise. Again, the healthcare provider could use the S.M.A.R.T. program and enroll his/her female patients in this program, only to have the Accutane prescription substituted at the

pharmacy level. In this scenario, the healthcare provider would be unaware of which product their female patient is actually taking throughout the course of her therapy. If experience is a guide, virtually all of the spontaneous adverse event reports will come into Roche. Therefore, there will have to be a mechanism in place that will ensure that these cases are correctly linked to the appropriate isotretinoin manufacturer without placing an undue burden on Roche.

4. EDUCATION, TRAINING, AND ROCHE EXPERTISE

Part of Roche's comprehensive pregnancy prevention risk management program includes a multi-faceted program for educating and training healthcare providers regarding the risks associated with Accutane therapy and the proper use and prescribing of the product in order to reduce or eliminate these risks. These educational services provided by Roche are exclusively focused on and created through our understanding of Accutane and the programs associated with Roche's isotretinoin product.

Roche has had many years of experience providing educational support to healthcare providers and patients through its scientifically trained field force and marketing department. As the S.M.A.R.T. program is rolled-out, Roche foresees an even greater need for medical education. Roche will provide healthcare providers with the "S.M.A.R.T. Guide to Best Practices" which was specifically designed to aid their proper use of Accutane.

If there are multiple isotretinoin products on the market, each with pregnancy prevention risk management materials and approaches to program support, healthcare providers will have the responsibility of assuring that their patients receive the correct information about the product and program prescribed and dispensed. Roche currently has trained Sales Specialists who will be providing instruction and guidance to healthcare providers regarding roll-out of the S.M.A.R.T. program, which is one of the key elements to encouraging and helping healthcare providers to make a smooth transition into joining and utilizing the S.M.A.R.T. program. Training brochures and educational materials for healthcare providers are also planned to assist the field force efforts.

Also critical to ensuring the success of S.M.A.R.T. is the roll-out of the program to the 56,000 pharmacies in the U.S. Again, Roche professionals will be key in training pharmacists and answering their questions, as well as providing training brochures and educational materials. These Roche professionals are a critical element to ensuring the smooth integration between pharmacists and healthcare providers and patients.

Working in concert with the FDA, Roche has developed and implemented training specifically designed for the Roche S.M.A.R.T. program. Roche has been providing voluntary CME/CEU programs to healthcare providers (physicians/nurses) to train them in pregnancy prevention and contraception. Many healthcare providers have benefited from this training, advancing the public health goals.

Additionally, any health care professional can contact the Roche Professional Service Center where an Accutane Pregnancy Safety Specialist will be available to help answer his/her questions regarding Accutane and pregnancy. These Specialists are trained Registered Nurse with several years' experience in both clinical practice and work in the Department of Drug Safety and Risk Management. These Specialists and the associated counseling services they provide have been in place for well over 15 years. Depending upon the nature of the question, or concern the health care professional poses, they assist

healthcare providers with all available resources regardless of exposure status of the pregnancy concerned. This may include literature searches, literature references, product information, and aggregate data from 20 years worldwide Accutane pregnancy safety experience.

In addition, the Specialists take a full patient history and help provide data which can assist the healthcare provider in assessing their patient's pregnancy risk. Extensive follow-up is also provided in the event the healthcare provider may require additional information, or if another specialist, involved in patient care could benefit from discussion with the Roche Specialist.

Roche is committed to continuing to provide these services to healthcare providers and patients but only when Accutane is dispensed.

4.1 Additional Educational Aspects of the S.M.A.R.T. Program

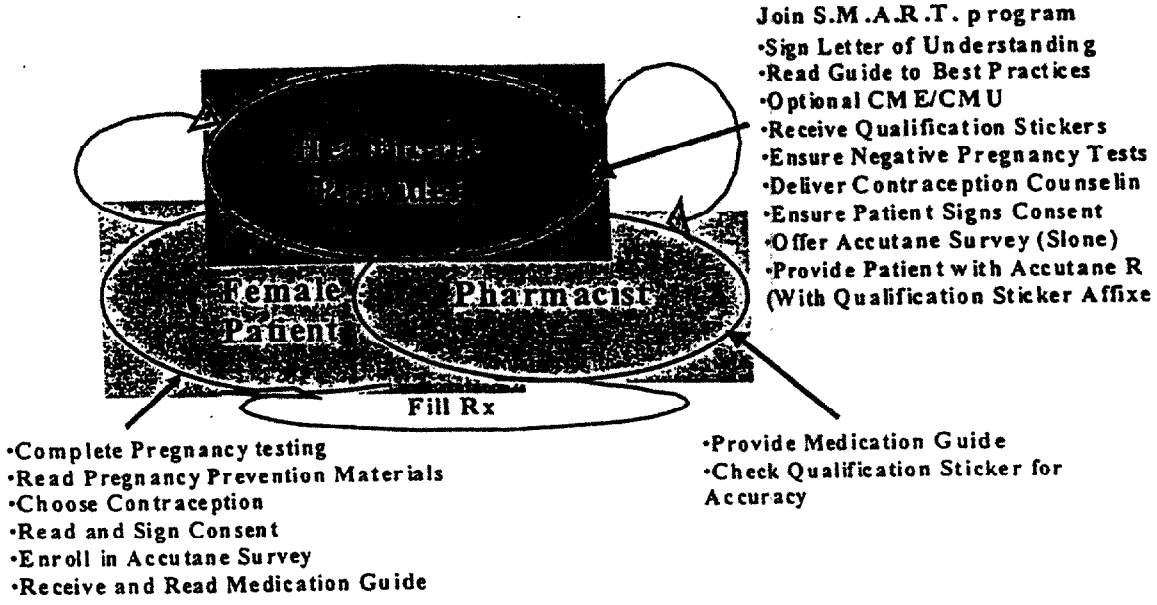
Roche provides an 800 number for patients to call with questions and/or concerns regarding contraception and pregnancy. The Roche Specialist continues to follow-up with the healthcare provider throughout the pregnancy course, through delivery, and throughout the first two years of the child's life. Finally, Roche also provides free contraceptive counseling to patients as listed in the Patient Information/Consent that is part of the Accutane package insert. The safety of patients using Accutane is our primary concern, and Roche will bear the full costs of either the Roche Specialist or the free contraceptive counseling and referrals, but only for prescriptions actually filled with Accutane.

4.2 Free Pregnancy Tests

Roche provides free pregnancy tests as part of the current pregnancy prevention risk management program for female Accutane patients for the initial, second, and monthly pregnancy testing during Accutane therapy. This offering is spelled out in the black box section of the Accutane package insert. This is done in order to facilitate obtaining the two negative pregnancy tests from potential female Accutane patients before the initial prescription of Accutane is written. Here as well, each manufacturer should bear the cost of pregnancy tests only for patients actually using their product.

5. CONCLUSION

For all of the reasons outlined in this document, Roche believes that it is essential to initiate discussions with FDA regarding the specifics as to how the Accutane pregnancy prevention risk management requirements will be applied to other manufacturers of isotretinoin products and how the S.M.A.R.T. and other pregnancy prevention risk management programs will be implemented and measured in a multiple-product environment to ensure the integrity of Roche's program.



Appendix 1: Accutane Pregnancy Prevention Risk Management Program

Program Elements

- Are you requiring all manufacturers to use Roche's copyrighted educational materials?
  - *Guide to Best Practices Brochure*
  - *Be Smart, Be Safe, Be Sure*
  - *Female and Male Patient Kit*
  - *Video*
  - *Story Board*
- Will all manufacturers be required to have all the educational pieces printed and approved prior to launch?
- Will all manufacturers be placing the medication guide in their package?
- Will all manufacturers be using the same text on their package as Roche?
- Are you requiring all manufacturers to use Roche's copyrighted pregnancy symbol?

Physician Database

- Will each manufacturer have to maintain a physician database and a Letter of Understanding?

Accutane Survey

- Will all manufacturers be required to have a survey protocol and questionnaire in place when marketed?
- Will that survey require the same:
  - methodology
  - design and questionnaires
  - analytic techniques
- Will all manufacturers need to demonstrate representativeness of their user population for the female survey?
- Will all manufacturers be required to enroll women in all three modes:
  - blister pack
  - physician's office (first line of contact, prior to receiving the prescription)
  - telephone

Accutane Survey

- The denominator for the survey is new female patient starts calculated the following way:

Exposed Females = (Rx) (% female)(30 days/# of Rx) (avg 1 female tx course/N days)

- How is the denominator for each manufacturer going to be calculated?

Questions Specific to Roche

- **Will our label be changed?**
  - Reprinting: PI, Be Smart,Be Safe,Be Sure; Informed Consent; Medical Guide; Guide to Best Practices; Letter of Understanding
- **Will our quarterly report change?**
  - Will all manufacturers be required to meet the same specifications of the quarterly pregnancy reports, as well as the annual pregnancy subsection of the periodic report?
  - special reporting of congenital abnormalities/anomalies on an expedited basis (i.e., 15 day)
- **Will all manufacturers be required to follow up with providers and patients during the course of their pregnancy and 2 years after birth?**
- **What are the plans for psychiatric risk management component(s) for other manufacturers?**
  - psychiatric brochure
  - psychiatric prospective clinical trial

Pharmacy Survey Outcome Measures

- Will the following four measures be required for all manufacturers?
  - Level of prescriber compliance w/ use of prescription qualification stickers (QSs)
  - Completeness of the information recorded on QSs
  - Level of pharmacy compliance w/ the dispensing recommendations for QSs
  - Comparison of prescription compliance rates for male and female patients

Pharmacy Survey Outcome Measures (cont'd.)

- Will all manufacturers have a protocol in place prior to launch?
- Will all protocols contain common elements?
  - Design/methods
  - Random samples
  - Analysis
  - Minimum of 10% audit of pharmacies
- Will all manufacturers have 4 waves over 2 years w/ metrics of 90% 1st year, and 100% 2nd year

Pharmacy Survey Outcome Measures (cont'd.)

- How is FDA going to ensure non-overlap of pharmacy samples in the audit?
- How is FDA going to minimize pharmacist frustration w/ audit sampling?
- Will all manufacturer's stickers have the same color and verbiage?